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Mild and efficient catalyst for nitrodopamine synthesis: from milligram to multi-gram scales

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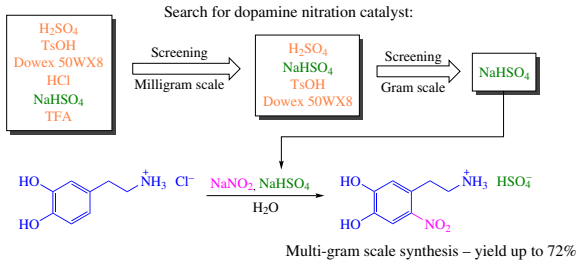
Sodium hydrogen sulfate is proposed as a mild acidic catalyst for the dopamine nitration with sodium nitrite. This reagent system gives nitrodopamine in high yield and excellent purity and is suitable for routine synthesis from milligram to multi-gram scale.



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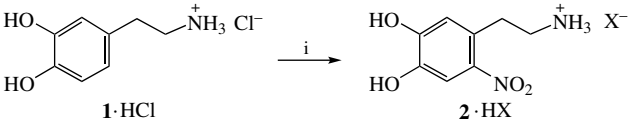
Dopamine **1** is a catechol amine compound that plays a pivotal role in the central nervous system as a neurotransmitter.[1] It is used extensively in research from biomedicine to the synthesis of functionalised nanoparticles and applied material science. For instance, a polymer adhesive with high adhesion based on polydopamine binds to many surfaces, such as metals, nanotubes, glasses, and ceramics.[2] In this respect, polydopamine is a biocompatible material for bone regeneration[3] and the development of cardiovascular stents.[4] The role of dopamine as a molecular anchor is crucial. Owing to the vicinal hydroxy groups, dopamine can bind to various metal ions (*e.g.*, iron and copper) forming complexes.[5,6] In this way, covalent modification of the surface of nanoparticles based on iron oxides using dopamine[6,7] is a popular tool in the design of various nanoscale systems, for example, targeted agents for the delivery of therapeutic drugs to tumour cells.

The electron-deficient dopamine derivative, nitrodopamine (ND) **2**, has several valuable properties in comparison to those of the initial dopamine **1**, such as increased binding to metal ions, resistance to oxidation and photolability.[8–10] Therefore, the investigation of simple and effective methods for the synthesis of ND seems essential for routine laboratory utilisation. This work was aimed to develop an optimal and alternative procedure for the nitration of dopamine **1** to ND **2** with a high degree of purity and high yield.

Different procedures of dopamine nitration have been published to date.[11–14] De la Breteche[15] reported the pH-dependent kinetics of the nitration of catechol amines, the formation of ND started at pH 6, and the dependence of the reaction rate of dopamine nitration with sodium nitrite in the pH range of 4–7.4 was established.[16] This work pointed out the growing reaction rate with the pH decrease, with additional acceleration in the presence of iron(III) chloride. Several catalysts among solid acids based on silica and polymers[17] were developed for green nitrating methods.

Firstly, we reproduced the well-known method[12] of dopamine **1** nitration in the presence of 20% sulfuric acid (Scheme 1). However, with the use of milligram amounts of the starting compound we failed in the precipitation of product **2** from the reaction mixture. Carrying out the reaction in an ice-cold bath with dropwise addition of a cooled sulfuric acid solution was also unsuccessful. Therefore, the screening of alternative acidic catalysts in aqueous medium without highly concentrated and aggressive acid solutions has been done. At the first stage, the selection of acid catalysts was carried out using small (milligram) amounts of starting dopamine **1** (see Scheme 1).†

For wide screening, 10 variants of the nitration procedure with $NaNO_2$ were tested (see Online Supplementary Materials, Table S1), namely, five sulfuric acid-catalysed experiments with the concentration range from 0.1 to 20%, and five experiments involving other proton-donor acids such as sodium hydrogen sulfate, *p*-toluenesulfonic acid, hydrochloric acid, trifluoroacetic acid and Dowex 50WX8 cation-exchange resin (hydrogen form, strongly acidic). The reaction times were 5 min, and the resulting



1·HCl **2**·HX

X = HSO_4, TsO, Cl, CF_3COO, polymer-SO_3

Scheme 1 *Reagents and conditions*: i, $NaNO_2$, acid catalyst, H_2O, ~5 °C, 1–30 min for catalyst addition, then 5 min.

† *General procedure for the screening of catalysts*. Dopamine hydrochloride **1**·HCl (0.010 g, 0.053 mmol, 1 equiv.) and $NaNO_2$ (0.013 g, 0.18 mmol, 3.5 equiv.) were dissolved in deionized water (150 μl) cooled in an ice bath to 0–5 °C. Then the catalyst (see Tables 1 and S1) was added to the reaction mixture under vigorous stirring over 30 min. An aliquot (20 μl) of reaction mixture was taken and analysed using LCMS.

Table 1 Results of screening assays: LCMS analysis of reaction mixtures.

Entry	Catalyst	Content of product **2** (%)		Number of components in the mixture	Content of dopamine **1** in the final mixture
		in (+) ions	in (–) ions		
1	0.1% H_2SO_4	40	23	5	Traces
2	1% H_2SO_4	67	76	6	Traces
3	5% H_2SO_4	54	72	7	No
4	10% H_2SO_4	49	57	12	No
5	20% H_2SO_4	76	77	10	No
6	TsOH	71	4.3	9	No
7	Dowex 50WX8	65	91	6	16% (+), 3.2% (–)
8	36% HCl	57	67	9	No
9	TFA	66	15	10	No
10	$NaHSO_4$	74	33	6	No

reaction mixtures were analysed by LCMS (Table 1). The catalysts were compared in terms of the content of mononitration product **2** in the mixture, as well as the presence of residual dopamine **1**. In general, good results were achieved with the application of 1% H_2SO_4, 5% H_2SO_4, Dowex 50WX8 and $NaHSO_4$ (entries 2, 3, 7 and 10). The product **2** content was quite high, and the total number of components in the mixtures did not exceed seven. Synthesis with 20% H_2SO_4 (entry 5) also provided high fraction of the target compound **2**, but the overall number of components in the mixture turned out to be higher in comparison to other catalysts. Finally, a 71% content (observed in positive ions) of nitrodopamine **2** was also reached with *p*-toluenesulfonic acid (entry 6). A significant amount of the original dopamine **1** remained in the mixture in the case of Dowex 50WX8 catalysis (entry 7). Unsatisfactory results were noted for HCl and TFA, such as a low ratio of **2** and numerous by-products (entries 8, 9). Unexpectedly, 10% H_2SO_4 did not show the proper catalytic efficiency (entry 4).

According to the results of the first part of the study, the following catalysts were chosen for the gram scale of the reaction: 1% H_2SO_4, 5% H_2SO_4, 20% H_2SO_4, TsOH, Dowex 50WX8 and $NaHSO_4$. The process was carried out in an ice-cooled aqueous solution with the addition of the acid catalyst to the stirred reaction mixture for 5 min. At the end of the reaction, the purity of the precipitates was analysed by LCMS in positive and negative ions (Table S3). The LCMS purity of the obtained precipitates correlates with the previous results of the above mentioned milligram scale reaction mixtures.

In cases with 20% H_2SO_4 and $NaHSO_4$, the precipitate formed spontaneously, whereas in other experiments the nitration product was precipitated from the reaction mixture only after neutralisation with $NaHCO_3$ solution to neutral pH. Mostly pure crude nitrodopamine **2** was obtained with the yield range 24–74%. Interestingly, the catalytic efficiencies of 5 and 20% H_2SO_4 solutions were comparable. The maximum yield of crude product **2** (74%) was obtained by catalysis with *p*-toluenesulfonic acid. However, according to LCMS results, the additional removal of the catalyst is needed in that case. Catalysis with sodium hydrogen sulfate turned out to be optimal in gram-scale synthesis of a pure nitrodopamine **2** in 53% yield without the need for further purification.

However, a significant excess of sodium nitrite as a nitrating agent (3.5 equiv.) in view of green chemistry can be considered as a disadvantage of this technique. Therefore, we tried to carry out a reaction with 1.1 equiv. of sodium nitrite in the presence of $NaHSO_4$. In this case, nitrodopamine did not precipitate neither spontaneously nor after treatment with $NaHCO_3$ solution. Further, we performed reactions using 2 and 3 equiv. of $NaNO_2$ when nitrodopamine **2** was obtained with 55 and 66% yields, respectively, demonstrating the possibility to decrease the amount of nitrating agent without loss in the formed product.

Mechanism of the described transformation involving the aromatic substitution has been reported previously.[18]

Finally, we conducted a multi-gram scale synthesis (on 10 g of initial dopamine hydrochloride) to prove the effectiveness of the developed procedure with $NaHSO_4$ and surprisingly the yield exceeded previous runs. Followed by the addition of sodium hydrogen sulfate, the final nitrodopamine **2** spontaneously precipitated and after drying *in vacuo* its yield was 72%.

In conclusion, we have tested and selected the optimal acid reagent to catalyse the reaction of dopamine with sodium nitrite. It has been shown that among the available and inexpensive reagents used, effective nitration catalysis occurs with the use of *p*-toluenesulfonic acid and sodium hydrogen sulfate. Sodium hydrogen sulfate, which is not inferior in efficiency and is superior in safety to the currently used 20% sulfuric acid, can be considered the optimal acid catalyst for the nitration of dopamine. The use of sodium hydrogen sulfate up to multi-gram scale synthesis provided high yield and purity of the resulting crude nitrodopamine without the need of chromatographic purification.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2024.02.034.

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